528,227

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number
WO 2004/026285 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number:
PCT/CA2003/001387

(22) International Filing Date:
19 September 2003 (19.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2,400,254 19 September 2002 (19.09.2002) CA

(71) Applicants *(for all designated States except US)*: **UNIVERSITY HEALTH NETWORK** [CA/CA]; 700 University Avenue, 8th Floor, Toronto, Ontario M5G 1X6 (CA). **AMGEN CANADA INC.** [CA/CA]; 6755 Mississauga Road, #400, Mississauga, Ontario L5N 7Y2 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CRACKOWER, Michael, A.** [CA/US]; 13137 E. Millerton Rd., Moorpark, CA 93021 (US). **PENNINGER, Josef, M.** [AT/AT]; Himmelhofgasse 62, A-1030 Vienna (AT).

(74) Agent: **BERESKIN & PARR**; 40 King Street West, 40th Floor, Toronto, Ontario M5H 3Y2 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

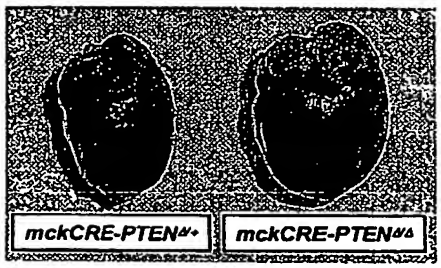
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/026285 A2

(54) Title: COMPOSITIONS AND METHODS FOR TREATING HEART DISEASE



(57) Abstract: The PTEN/PI3K signaling pathway regulates a vast array of fundamental cellular responses. We show that cardiomyocyte-specific inactivation of tumor suppressor PTEN results in hypertrophy, and unexpectedly, a dramatic decrease in cardiac contractility. Analysis of double mutant mice revealed that the cardiac hypertrophy and the contractility defects can be genetically uncoupled. PI3Kγ mediates the alteration in cell size while PI3Kγ acts as a negative regulator of cardiac contractility. Mechanistically, PI3Kγ inhibits cAMP production and hypercontractility can be reverted by blocking cAMP function. These data show that PTEN has an important *in vivo* role in cardiomyocyte hypertrophy and GPCR signaling and identify a function for the PTEN-PI3Kγ pathway in the modulation of heart muscle contractility.